PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 19 October 2000 (19.10.00)	
International application No. PCT/FI00/00131	**Applicant's or agent's file reference** FIBRE
International filing date (day/month/year) 21 February 2000 (21.02.00)	**Priority date** (day/month/year) 22 February 1999 (22.02.99)
Applicant JOKINEN, Mika et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:
15 September 2000 (15.09.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer R. E. Stoffel
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

FI0000131

Form PCT/IB/331 (July 1992)

Copy for the designated Office (DO/US)

PCT/FI00/00131

TENT COOPERATION TRE Y

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

TURUN PATENTTITOIMISTO OY
P.O. Box 99
FIN-20521 Turku
FINLANDE

Date of mailing (day/month/year)
11 October 2000 (11.10.00)

Applicant's or agent's file reference
FIBRE

IMPORTANT NOTIFICATION

International application No.
PCT/FI00/00131

International filing date (day/month/year)
21 February 2000 (21.02.00)

1. The following indications appeared on record concerning:

[ ] the applicant [ ] the inventor [X] the agent [ ] the common representative

Name and Address

ORION CORPORATION
Orion Pharma
Industrial Property Rights
P.O. Box 65
FIN-02101 Espoo
Finland

State of Nationality | State of Residence

Telephone No.
+358-9-429 2926

Facsimile No.
+358-9-429 3477

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [X] the name [X] the address [ ] the nationality [ ] the residence

Name and Address

TURUN PATENTTITOIMISTO OY
P.O. Box 99
FIN-20521 Turku
Finland

State of Nationality | State of Residence

Telephone No.
+358-2-274 1555

Facsimile No.
+358-2-274 1556

Teleprinter No.

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[X] the International Searching Authority
[ ] the International Preliminary Examining Authority
[X] the designated Offices concerned
[ ] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer
C. Cupello

Telephone No.: (41-22) 338.83.38

003576441

Copy for the Elected Office (EO/US)

PATENT COOPERATION TREATY

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PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

TURUN PATENTTITOIMISTO OY
P.O. Box 99
FIN-20521 Turku
FINLANDE

Date of mailing (day/month/year) 31 August 2001 (31.08.01)	
Applicant's or agent's file reference AP100039	**IMPORTANT NOTIFICATION**
International application No. PCT/FI00/00131	**International filing date** (day/month/year) 21 February 2000 (21.02.00)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [ ] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
BIOXID OY Tykistökatu 4 D, 4. krs FIN-20520 Turku Finland	FI	FI
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:
New applicant for all designated States except US. JOKINEN, Mika, PELTOLA, Timo, VEITTOLA, Sinikka, AHOLA, Manja and KORTESUO, Pirjo are now applicant/inventors for US only.Please also note that the agent's file reference has been corrected.

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer François BAECHLER
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

004254382

Form PCT/IB/306 (March 1994)

Translation

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

3

Applicant's or agent's file reference 99/037 WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/CH00/00101	International filing date (*day/month/year*) 24 February 2000 (24.02.00)	Priority date (*day/month/year*) 01 March 1999 (01.03.99)
International Patent Classification (IPC) or national classification and IPC G01F 1/68		
Applicant ABB RESEARCH LTD.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
02 October 2000 (02.10.00)	09 April 2001 (09.04.2001)
Name and mailing address of the IPEA/EP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/CH00/00101

I. Basis of the report

1. This report has been drawn on the basis of (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

☐ the international application as originally filed.

☒ the description, pages 1-12, as originally filed,
pages _____, filed with the demand,
pages _____, filed with the letter of _____,
pages _____, filed with the letter of _____.

☒ the claims, Nos. 1-10, as originally filed,
Nos. _____, as amended under Article 19,
Nos. _____, filed with the demand,
Nos. _____, filed with the letter of _____,
Nos. _____, filed with the letter of _____.

☒ the drawings, sheets/fig 1/1, as originally filed,
sheets/fig _____, filed with the demand,
sheets/fig _____, filed with the letter of _____,
sheets/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/fig _____

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	3,6-10	YES
	Claims	1,2,4,5	NO
Inventive step (IS)	Claims		YES
	Claims	1-10	NO
Industrial applicability (IA)	Claims	1-10	YES
	Claims		NO

2. Citations and explanations

1. This report makes reference to the following documents:

D1: EP-A-0 784 200 (LANDIS & GYR TECH INNOVAT) 16 July 1997 (1997-07-16)

D2: WO-A-98/36247 (VOGT HOLGER; KERSJES RALF (DE); MOKWA WILFRIED (DE); ZIMMER GUENTE) 20 August 1998 (1998-08-20)

D3: EP-A-0 373 965 (HONEYWELL INC) 20 June 1990 (1990-06-20)

D4: GB-A-1 463 507 (AGAR INSTR) 2 February 1977 (1977-02-02)

D5: US-A-5 220 830 (BONNE ULRICH) 22 June 1993 (1993-06-22).

2. Novelty and inventive step:

D1 discloses a gas meter as per Claims 1 and 2: the anemometer consists of temperature measuring elements (diodes) 8,9 and heating element 10 (Figure 2). (The term "anemometer" is used in column 4, line 58).

Claims 1 and 2 are also known from D3 - see in particular page 3, lines 43-46 and page 4, lines 31-

34.

Claims 1 and 2 are also known from D5 - see in particular column 4, lines 66-68.

The other dependent claims clearly do not contain any additional features involving an inventive step, since they either result from the subject matter of Claim 1 or relate to routine design procedures that a person skilled in the art would use according to the circumstances:

Claim 3: CMOS anemometers are known from the articles cited in the application and from D2, and would be straightforward for a person skilled in the art, especially since the resulting advantages are readily foreseeable. Consequently the subject matter of Claim 3 does not involve an inventive step either.

Claim 4: known from D1 - see Figure 1.

Claim 5: known from D5 - see abstract (line 8 "particulate trapping system").

Claim 6: see D4, page 6, lines 68-83.

Claims 7-10: obvious alternatives.

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

Contrary to PCT Rule 5.1(a)(ii), the description does not cite documents D1, D2, D3, D4 or D5, or indicate the relevant prior art disclosed therein.

PATENT COOPERATION TREATY

REC'D 15 MAY 2001

WIPO

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70) 14

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
FIBRE		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/FI00/00131	21/02/2000	22/02/1999
International Patent Classification (IPC) or national classification and IPC C03B37/00		
Applicant JOKINEN, Mika		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15/09/2000	11.05.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Munro, B Telephone No. +49 89 2399 8529

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/FI00/00131

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-18 as originally filed

Claims, No.:

1-29 with telefax of 19/04/2001

Drawings, sheets:

1/14-14/14 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 28, 29 as regards IA.

because:

   ☒ the said international application, or the said claims Nos. 28, 29 relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

   Novelty (N) Yes: Claims 3, 4, 6, 7, 18, 19, 22, 23

	No:	Claims	1, 2, 5, 8-17, 20, 21, 24-29
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-29
Industrial applicability (IA)	Yes:	Claims	1-27
	No:	Claims	-

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Section III

1. Claims 28 and 29 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

   Note: The EPO does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Section V

2. Reference is made to the following documents:

   D1: DE 196 09 551 C
   D7: WO 97 45367 A

3. The examination with regard to novelty and inventive step was conducted in light of the description and in light of the comments in Section VIII.

4. The subject-matter of claims 1, 2, 5, 8-17, 20, 21 and 24-29 does not fulfil the requirements of Article 33(2) PCT.

4.1 The subject-matter of claims 1, 12, 16 and 20 is not new, because D1 (whole document) discloses a method for preparing biodegradable silica fibres, whereby spinning first begins after the sol has been stored long enough for it to be spinnable.
Furthermore, the subject-matter of claims 1, 2, 5, 16, 17, 20 and 21 is not new, because D7 (whole document, especially the claims) discloses a method for producing biodegradable silica fibres by a spinning process, whereby the viscosity at the starting point for spinning is below 100 000 mPaS (see D7, example 2).

4.2 The subject-matter of claims 8-15 are not new, because D1 (whole document) and D7 (examples 2 and 3, claims) disclose biodegradable silica fibres obtained from a sol.
The dependent claims were considered as not containing any further limiting features (see Section VIII).

4.3 The subject-matter of claims 24-29 is not new, because of the disclosure of D7 (claims).

5. The subject-matter of claims 3, 4, 6, 7, 18, 19, 22 and 23 does not fulfil the requirements of Article 33(3) PCT. The subject-matter of these claims does not involve an inventive step, the reasoning is as follows:
Document D1 is considered to be the closest prior art, because D1 (whole document) discloses a method for preparing biodegradable silica fibres, whereby spinning first begins after the sol has been stored long enough for it to be spinnable. Furthermore, D1 (col. 6, l. 18-22) discloses that the viscosity of the sol after preparation is between 50 and 50000 mPas, preferably 500 to 3000 mPas. The sol thus obtained is then filtered and then stored until the viscosity increases enough to give a spinnable sol, whilst avoiding gelation. The viscosity of the sol is therefore preferably greater than 500 mPas at the time of spinning. The claims of the application under consideration specify a viscosity of 1000- 50000 mPas, preferably 2000-15 000 mPas.
The only difference between the process according to D1 and the process according is that in D1 the viscosity at the starting point of spinning is not specified.
However, person skilled in the art would realise from D1 that the working viscosity range should be preferably between 500 mPas and the point of gelation. The person skilled in the art, having knowledge of D1, would work in a viscosity range which overlaps with those defined in claims 3, 4, 6, 7, 18, 19, 22 and 23. The person skilled in the art would thus tend to work under the same conditions and would thus arrive at the invention claimed without having to exercise inventive ingenuity.

Section VIII

6. The subject-matter of claims 1 and 8-15 does not fulfil the requirements of Article 6 PCT.

6.1 The subject-matter of claims 1 and 8-15 is not clear, because the term "controllably biodegradable" is vague and indefinite in scope. A claim should not include vague or equivocal forms of wording which leave the reader in doubt as to the exact scope of a feature. The method of determination of the parameter "biodegradable" is not defined in the claim. Furthermore, it is not clear exactly what is meant by "controllably". Does the term "controllably biodegradable" mean that the biodegradability can be adjusted between certain limits or does it mean that the fibres biodegrade at a constant rate etc.? Features which are intended to serve as distinguishing features should be adequately defined in the independent claim(s).

For the purposes of examination, this feature was not considered as being limiting.

6.2 The viscosity values (cls. 2-7, 9-11, 13-15, 17-19 and 21-23) are not clear (Art. 6, PCT), because the measured value of viscosity depends on the exact method of measurement used (eg. apparatus, temperature). Therefore, for the purposes of examination, the viscosity values were considered to be not limited to specific measuring conditions.

6.3 Note: The subject-matter of claims 8 - 15 is directed towards product-by-process claims. Only those product features, which are discernible from the subject-matter of claims 8 - 15 were considered for the purposes of examination.

6.4 The statement on page 6, l. 22-24 casts doubt on the intended scope. For the purposes of examination the term "spinning" was also interpreted as encompassing "drawing".

CLAIMS

1. A method for preparing a controllably biodegradable silica fibre, comprising spinning the fibre from a silica sol, wherein the starting point of the spinning process is controlled by the viscosity of the silica sol.

2. The method according to claim 1 wherein the viscosity of the silica sol at the starting point of the spinning process is below 100 000 Pas.

3. The method according to claim 2 wherein the viscosity of the silica sol at the starting point of the spinning process is from about 1000 to about 50 000 mPas.

4. The method according to claim 3 wherein the viscosity of the silica sol at the starting point of the spinning process is from about 2000 to about 15 000 mPas.

5. A method for preparing a controllably biodegradable fibre, comprising spinning the fibre from a spinning sol having a viscosity below 100 000 mPas.

6. The method according to claim 5 wherein the viscosity of the spinning sol is from about 1000 to about 50 000 mPas

7. The method according to claim 6 wherein the viscosity of the spinning sol is from about 2000 to about 15 000 mPas.

8. A controllably biodegradable silica fibre spun from silica sol, the biodegradation of said fibre being controlled by controlling the starting point of the spinning process by the viscosity of the silica sol.

9. The controllably biodegradable fibre according to claim 8, wherein the viscosity of the silica sol at the starting point of the spinning process is below 100 000 mPas.

10. The controllably biodegradable fibre according to claim 9, wherein the viscosity of the silica sol at the starting point of the spinning process is from about 1000 to about 50 000 mPas.

11. The controllably biodegradable fibre according to claim 10, wherein the viscosity of the silica sol at the starting point of the spinning process is from about 2000 to about 15 000 mPas.

12. A controllably biodegradable silica fibre spun from a silica sol, the biodegradation of the fibre being controlled by controlling the viscosity of the spinning sol.

13. The controllably biodegradable fibre according to claim 12, wherein the viscosity of the spinning sol is below 100 000 mPas.

14. The controllably biodegradable fibre according to claim 13, wherein the viscosity of the spinning sol is from about 1000 to about 50 000 mPas.

15. The controllably biodegradable fibre according to claim 14, wherein the viscosity of the spinning sol is from about 2000 to about 15 000 mPas.

16. A method for controlling the biodegradation of a silica fibre spun from a silica sol, wherein by the method comprises controlling the viscosity of the spinning sol.

17. The method according to claim 16 wherein the viscosity of spinning sol is below 100 000 mPas.

18. The method according to claim 17 wherein the viscosity of spinning sol is from about 1000 to about 50 000 mPas.

19. The method according to claim 18 wherein the viscosity of spinning sol is from about 2000 to about 15 000 mPas.

20. A method for controlling the biodegradation of a silica fibre spun from a silica sol, wherein the method comprises controlling the viscosity of the silica sol at starting point of the spinning process.

21. The method according to claim 20 wherein the viscosity of the silica sol at the starting point of the spinning process is below 100 000 mPas.

22. The method according to claim 21 wherein the viscosity of the silica sol at the starting point of the spinning process is from about 1000 to about 50 000 mPas.

23. The method according to claim 22 wherein the viscosity of the silica sol at the starting point of the spinning process is from about 2000 to about 15 000 mPas.

24. A delivery device comprising the controllably biodegradable fibre according to any one of claims 8 – 15, wherein the fibre contains a biologically active agent.

25. The delivery device according to claim 24, wherein said biologically active agent is a medicine, a protein, a hormone, a living or dead cell, a bacteria, a virus or a part thereof.

26. The delivery device according to claim 25, wherein said biologically active agent is a medicine.

27. A pharmaceutical preparation comprising a delivery device according to any one of claim 24-26 .

28. A method for administering a biologically active agent into a human or animal, wherein said method comprises implanting, injecting , or mucosally attaching a delivery device, wherein said delivery device comprises a controllably biodegradable fibre and wherein the fibre comprises a biologically active agent.

29. The method according to claim 28, wherein the biologically active agent is administred into a mammal.

CLAIMS

1. A method for preparing a controllably biodegradable silica fibre, comprising spinning the fibre from a silica sol, wherein the starting point of the spinning process is controlled by the viscosity of the silica sol.

2. The method according to claim 1 wherein the viscosity of the silica sol at the starting point of the spinning process is below 100 000 mPas.

3. The method according to claim 2 wherein the viscosity of the silica sol at the starting point of the spinning process is from about 1 000 to about 50 000 mPas.

4. The method according to claim 3 wherein the viscosity of the silica sol at the starting point of the spinning process is from about 2 000 to about 15 000 mPas.

5. A method for preparing a controllably biodegradable fibre, comprising spinning the fibre from a spinning sol having a viscosity below 100 000 mPas.

6. The method according to claim 5 wherein the viscosity of the spinning sol is from about 1 000 to about 50 000 mPas.

7. The method according to claim 6 wherein the viscosity of the spinning sol is from about 2 000 to about 15 000 mPas.

8. A controllably biodegradable silica fibre spun from silica sol, the biodegradation of said fibre being controlled by controlling the starting point of the spinning process by the viscosity of the silica sol.

9. The controllably biodegradable fibre according to claim 8, wherein the viscosity of the silica sol at the starting point of the spinning process is below 100 000 mPas.

10. The controllably biodegradable fibre according to claim 9, wherein the viscosity of the silica sol at the starting point of the spinning process is from about 1 000 to about 50 000 mPas.

11. The controllably biodegradable fibre according to claim 10, wherein the viscosity of the silica sol at the starting point of the spinning process is from about 2 000 to about 15 000 mPas.

12. A controllably biodegradable silica fibre spun from a silica sol, the biodegradation of the fibre being controlled by controlling the viscosity of the spinning sol.

13. The controllably biodegradable fibre according to claim 12, wherein the viscosity of the spinning sol is below 100 000 mPas.

14. The controllably biodegradable fibre according to claim 13, wherein the viscosity of the spinning sol is from about 1 000 to about 50 000 mPas.

15. The controllably biodegradable fibre according to claim 14, wherein the viscosity of the spinning sol is from about 2 000 to about 15 000 mPas.

16. A method for controlling the biodegradation of a silica fibre spun from a silica sol, wherein the method comprises controlling the viscosity of the spinning sol.

17. The method according to claim 16 wherein the viscosity of the spinning sol is below 100 000 Pas.

18. The method according to claim 17 wherein the viscosity of the spinning sol is from about 1 000 to about 50 000 mPas.

19. The method according to claim 18 wherein the viscosity of the spinning sol is from about 2 000 to about 15 000 mPas.

20. A method for controlling the biodegradation of a silica fibre spun from a silica sol, wherein the method comprises controlling the viscosity of the silica sol at the starting point of the spinning process.

21. The method according to claim 20 wherein the viscosity of the silica sol at the starting point of the spinning process is below 100 000 mPas.

22. The method according to claim 21 wherein the viscosity of the silica sol at the starting point of the spinning process is from about 1 000 to about 50 000 mPas.

23. The method according to claim 22 wherein the viscosity of the silica sol at the starting point of the spinning process is from about 2 000 to about 15 000 mPas.

24. A delivery device comprising the controllably biodegradable fibre according to any one of claims 8–15, wherein the fibre contains a biologically active agent.

25. The delivery device according to claim 24, wherein said biologically active agent is a medicine, a protein, a hormone, a living or dead cell, a bacteria, a virus or a part thereof.

26. The delivery device according to claim 25, wherein said biologically active agent is a medicine.

27. A pharmaceutical preparation comprising a delivery device according to any one of claims 24–26.

28. A method for administering a biologically active agent into a human or animal, wherein said method comprises implanting, injecting, or mucosally attaching a delivery device, wherein said delivery device comprises a controllably biodegradable fibre according to any of claims 8–15 and wherein the fibre comprises a biologically active agent.

29. The method according to claim 28, wherein the biologically active agent is administered into a mammal.

PATENT COOPERATION TREATY

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15 MAY 2001
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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

TURUN PATENTTITOIMISTO OY
P.O.Box 99
20521 Turku
FINLANDE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

	Date of mailing *(day/month/year)* 11.05.2001
Applicant's or agent's file reference FIBRE FP 100039	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/FI00/00131	21/02/2000	22/02/1999

Applicant
JOKINEN, Mika

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Christensen, J Tel.+49 89 2399-8052

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
FIBRE		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/FI00/00131	21/02/2000	22/02/1999
International Patent Classification (IPC) or national classification and IPC C03B37/00		
Applicant JOKINEN, Mika		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15/09/2000	11.05.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Munro, B Telephone No. +49 89 2399 8529

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/FI00/00131

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-18 as originally filed

Claims, No.:

1-29 with telefax of 19/04/2001

Drawings, sheets:

1/14-14/14 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 28, 29 as regards IA.

because:

☒ the said international application, or the said claims Nos. 28, 29 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N) Yes: Claims 3, 4, 6, 7, 18, 19, 22, 23

	No:	Claims	1, 2, 5, 8-17, 20, 21, 24-29
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-29
Industrial applicability (IA)	Yes:	Claims	1-27
	No:	Claims	-

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Section III

1. Claims 28 and 29 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

   Note: The EPO does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Section V

2. Reference is made to the following documents:

   D1: DE 196 09 551 C
   D7: WO 97 45367 A

3. The examination with regard to novelty and inventive step was conducted in light of the description and in light of the comments in Section VIII.

4. The subject-matter of claims 1, 2, 5, 8-17, 20, 21 and 24-29 does not fulfil the requirements of Article 33(2) PCT.

4.1 The subject-matter of claims 1, 12, 16 and 20 is not new, because D1 (whole document) discloses a method for preparing biodegradable silica fibres, whereby spinning first begins after the sol has been stored long enough for it to be spinnable.
Furthermore, the subject-matter of claims 1, 2, 5, 16, 17, 20 and 21 is not new, because D7 (whole document, especially the claims) discloses a method for producing biodegradable silica fibres by a spinning process, whereby the viscosity at the starting point for spinning is below 100 000 mPaS (see D7, example 2).

4.2 The subject-matter of claims 8-15 are not new, because D1 (whole document) and D7 (examples 2 and 3, claims) disclose biodegradable silica fibres obtained from a sol.
The dependent claims were considered as not containing any further limiting features (see Section VIII).

4.3 The subject-matter of claims 24-29 is not new, because of the disclosure of D7 (claims).

5. The subject-matter of claims 3, 4, 6, 7, 18, 19, 22 and 23 does not fulfil the requirements of Article 33(3) PCT. The subject-matter of these claims does not involve an inventive step, the reasoning is as follows:
Document D1 is considered to be the closest prior art, because D1 (whole document) discloses a method for preparing biodegradable silica fibres, whereby spinning first begins after the sol has been stored long enough for it to be spinnable. Furthermore, D1 (col. 6, l. 18-22) discloses that the viscosity of the sol after preparation is between 50 and 50000 mPas, preferably 500 to 3000 mPas. The sol thus obtained is then filtered and then stored until the viscosity increases enough to give a spinnable sol, whilst avoiding gelation. The viscosity of the sol is therefore preferably greater than 500 mPas at the time of spinning. The claims of the application under consideration specify a viscosity of 1000- 50000 mPas, preferably 2000-15 000 mPas.
The only difference between the process according to D1 and the process according is that in D1 the viscosity at the starting point of spinning is not specified.
However, person skilled in the art would realise from D1 that the working viscosity range should be preferably between 500 mPas and the point of gelation. The person skilled in the art, having knowledge of D1, would work in a viscosity range which overlaps with those defined in claims 3, 4, 6, 7, 18, 19, 22 and 23. The person skilled in the art would thus tend to work under the same conditions and would thus arrive at the invention claimed without having to exercise inventive ingenuity.

Section VIII

6. The subject-matter of claims 1 and 8-15 does not fulfil the requirements of Article 6 PCT.

6.1 The subject-matter of claims 1 and 8-15 is not clear, because the term "controllably biodegradable" is vague and indefinite in scope. A claim should not include vague or equivocal forms of wording which leave the reader in doubt as to the exact scope of a feature. The method of determination of the parameter "biodegradable" is not defined in the claim. Furthermore, it is not clear exactly what is meant by "controllably". Does the term "controllably biodegradable" mean that the biodegradability can be adjusted between certain limits or does it mean that the fibres biodegrade at a constant rate etc.? Features which are intended to serve as distinguishing features should be adequately defined in the independent claim(s).

For the purposes of examination, this feature was not considered as being limiting.

6.2 The viscosity values (cls. 2-7, 9-11, 13-15, 17-19 and 21-23) are not clear (Art. 6, PCT), because the measured value of viscosity depends on the exact method of measurement used (eg. apparatus, temperature). Therefore, for the purposes of examination, the viscosity values were considered to be not limited to specific measuring conditions.

6.3 Note: The subject-matter of claims 8 - 15 is directed towards product-by-process claims. Only those product features, which are discernible from the subject-matter of claims 8 - 15 were considered for the purposes of examination.

6.4 The statement on page 6, l. 22-24 casts doubt on the intended scope. For the purposes of examination the term "spinning" was also interpreted as encompassing "drawing".

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(71)(72) Applicants and Inventors: JOKINEN, Mika [FI/FI]; Mielikinkatu 5, FIN-20540 Turku (FI). PELTOLA, Timo [FI/FI]; Jaakkimankatu 5 D 33, FIN-20740 Turku (FI). VEITTOLA, Sinikka [FI/FI]; Elementinpolku 17 B 24, FIN-33720 Tampere (FI). AHOLA, Manja [FI/FI]; Iltatähdentie 4 as 91, FIN-20200 Turku (FI). KORTESUO, Pirjo [FI/FI]; Pohjantähdentie 4 B 38, FIN-20200 Turku (FI).

(74) Agent: ORION CORPORATION; Orion Pharma, Industrial Property Rights, P.O. Box 65, FIN-02101 Espoo (FI).

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(54) Title: BIODEGRADABLE CERAMIC FIBRES FROM SILICA SOLS

(57) Abstract

The present invention relates to a method for preparing controllably biodegradable silica fibres. The method comprises spinning the fibres from a silica sol, the viscosity of the sol being controlled. Further, the present invention relates to controllably biodegradable silica fibres prepared according to the invention and methods for controlling the biodegradability of the fibres. The invention also relates to controllably biodegradable fibres as sustained and/or controlled release delivery devices for biologically active agents, and to pharmaceutical preparations comprising such devices.

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BIODEGRADABLE CERAMIC FIBRES FROM SILICA SOLS

TECHNICAL FIELD OF THE INVENTION

The present invention is directed to methods for preparing controllably biodegradable silica fibres. Specifically, the present invention is directed to methods for preparing controllably biodegradable silica fibres comprising spinning the fibres from a silica sol, the viscosity of the sol being controlled. Further, the invention is directed to controllably biodegradable silica fibres prepared according to the present invention. The invention is further directed to methods for controlling the biodegradation of the silica fibres. The invention is also directed to controllably biodegradable fibres as sustained and/or controlled release delivery devices for biologically active agents, especially medicines, proteins, or hormones, and to pharmaceutical preparations comprising the devices.

BACKGROUND OF THE INVENTION

The sol-gel derived ceramic materials have many applications in various fields. Bioceramics is one of the most promising and interesting fields that still need much development work for optimizing the properties of the material in the biological environment. The sol-gel process starting from a liquid phase enables an easy control of the pore structure of the material and an introduction of other components in different kinds of composites, especially, in the case of silica-based materials. The processing of the sol-gel derived silica fibres is known, and the main parameters controlling the process are the functionality of the silica precursors, or the degree of branching of the silica clusters. The latter critically affects the spinnability and has commonly been characterised by rheological measurements.

Fibres have traditionally been used to improve mechanical properties of materials. In the case of the sol-gel derived silica fibres, there are two main parameters that determine the fibre bulk structure. Heat treatment of the fibres is one way to condense the bulk structure. Depending on the application of the sol-gel

derived biodegradable silica fibres, the balance between mechanical properties and biodegradation may vary. For example, the mechanical properties are of minor importance when the silica fibre is used as a drug delivery device in a soft tissue. However, the mechanical properties have to be good enough to further process the obtained fibres to a desired form after spinning. The biodegradation of the silica fibre decreases remarkably after heat-treatment at high temperatures simultaneously as the mechanical properties become better.

International patent publication No. WO 97/45367 discusses sol-gel produced silica-xerogel materials. Patent publication DE 19609551 discusses silica fibers obtained by drawing them from a specific spinning composition. Neither of the patent publications teaches or suggests a controllably biodgradable silica fibre, a delivery device, or a pharmaceutical composition according to the invention or methods for preparing or using the same. Further, neither of the patent publications teaches or suggests a method according to the invention for controlling the biodegradation of a silica fibre.

SUMMARY OF THE INVENTION

It has been found that the biodegradation of silica fibres can be controlled by controlling the viscosity of the spinning solution and, thus, the biodegradation of the silica fibres can be varied even when the same recipe is used. Accordingly, an object of the present invention is to provide a method for preparing controllably biodegradable silica fibres. Specifically, the present invention provides a method for preparing a controllably biodegradable silica fibre, wherein the method comprises spinning the fibre from a silica sol, wherein the viscosity of the silica sol is controlled. More specifically, the present invention provides a method for preparing a controllably biodegradable silica fibre, wherein the method comprises spinning the fibre from a silica sol, wherein the starting point of the spinning process is controlled by the viscosity of the silica sol.

It should be noted that the term spinning encompasses all of the suitable methods for preparing silica fibres from a silica sol.

A further object of the invention is to provide a controllably biodegradable silica fibre spun from a silica sol. Specifically, the present invention provides a controllably biodegradable silica fibre spun from a silica sol, wherein the biodegradation of the fibre is controlled by controlling the viscosity of the spinning sol. More specifically, the present invention provides a controllably biodegradable silica fibre spun from a silica sol having a viscosity below 100 000 mPas (milliPascalsecond), preferably having a viscosity of 1000 - 50 000 mPas, and more preferably of 2000 - 15 000 mPas. The fibre of the present invention is preferably heat-treated, to initially dry the fibre, only at low temperatures not harmful to biologically active agents, and it is not otherwise externally densified.

A further object of the invention is to provide sustained and/or controlled release delivery devices for biologically active agents, especially medicines, proteins, or hormones which are made of controllably biodegradable silica fibres, and pharmaceutical preparations comprising said devices.

A further object of the present invention is a method for controlling the biodegradation of silica fibres. The method comprises controlling the viscosity of the spinning sol or controlling the viscosity of the silica sol at the starting point of the spinning process.

Also, an object of the present invention is to provide a method for administering a biologically active agent to a human or animal which comprises implanting, injecting, or mucosally attaching to a human or animal a delivery device made of controllably biodegradable silica fibres of the present invention, in which structure a biologically active agent is incorporated.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a thermogravimetric spectra of the green state fibre samples aged for 3 months.

Figure 2 shows a derivative of the thermogravimetric spectra of Figure 1.

Figure 3 shows an FT-IR spectra of the fibre samples heat-treated in the thermogravimetric analysis.

Figure 4 shows a transmission electron micrograph of the green body of FIB2_B aged for 3 months.

Figure 5 shows the spinning viscosity as a function of the starting point of the spinning process for fibres FIB1, FIB2 and FIB3. Closed square (■) aged for 1 month, open square (□) aged for 2 months, closed triagle (▲) aged for 1 month and for 3 months, closed circle (●) aged for 1 month, 3 months and 5 months, open circle (○) aged for 4 months, asterisk (✱) aged for 6 months.

Figure 6 shows the biodegradation of the green state fibres aged for 3 months. Closed square (■) FIB1_A, open square (□) FIB1_B, closed circle (●) FIB2_A, open circle (○) FIB2_B, asterisk (✳) FIB3.

Figure 7 shows the SiO_2 solubility measured as saturation level of silica in SBF as a function of sol viscosity at the starting point of the spinning process for FIB1 aged for various time periods.

Figure 8 shows the SiO_2 solubility in weight-% per hour in SBF as a function of sol viscosity at the starting point of the spinning process for FIB1 aged for various time periods.

Figure 9 shows the SiO_2 solubility measured as saturation level of silica in SBF as a function of sol viscosity at the starting point of the spinning process for FIB2 aged for various time periods.

Figure 10 shows the SiO_2 solubility in weight-% per hour in SBF as a function of sol viscosity at the starting point of the spinning process for FIB2 aged for various time periods.

Figure 11 shows the SiO_2 solubility measured as saturation level of silica in SBF as a function of sol viscosity at the starting point of the spinning process for FIB3 aged for various time periods.

Figure 12 shows the SiO_2 solubility in weight-% per hour in SBF as a function of sol viscosity at the starting point of the spinning process for FIB3 aged for various time periods.

Figure 13 shows the changes of SiO_2 concentration (wt-%) as a function of immersion time in the simulated body fluid for different fibres.

Figure 14 shows the release of dexmedetomidine from the silica fibres of Example 4. Closed circle (●) 5600 - 7500 mPas, asterisk (⊠) 11 500 – 14900 mPas, open triangle (Δ) 17 000-29 000 mPas, closed square (■) 39 000 –100 000 Pas.

DESCRIPTION OF THE INVENTION

Applicants have discovered that the biodegradation of silica fibres can be controlled by controlling the viscosity of the spinning solution. The biodegradation of the fibres can be varied even when using the same recipe. The biodegradation of the fibres can be adjusted for desired purposes by controlling the viscosity of the spinning solution for determining the starting point of the spinning.

Factors affecting the viscosity are the stage of spinnability, the temperature of the silica sol and the amount of solvent in the spinning sol. The silica sol is spinnable within a certain time period, rather than at a single point, and the viscosity of the silica sol increases during that time period. In the earlier stage of spinnability the silica polymers are somewhat smaller and they are packed easier forming denser structures than the larger silica polymers of the later stage of spinnability. In addition, higher viscosity inhibits the orientation of the silica polymers leaving the structure more open. The fibres spun in the early stage of the spinnability period degrade more slowly in the simulated body fluid than the fibres spun in the later stage of the spinnability. The stage of spinnabilty may differ depending on the spinning method. Another parameter that controls the spinnability and the viscosity is the temperature of the silica sol which can be varied. The fibres spun from the silica sols having higher viscosity at a lower temperature (e.g., 0 °C) degrade faster than the corresponding fibres spun at higher temperatures (e.g., 20 °C).

The method for preparing a controllably biodegradable fibre of the present invention comprises spinning the fibre from a silica sol, wherein the starting point of the spinning process is controlled by the viscosity of the silica sol. The viscosity of the silica sol at the starting point of the spinning process is below 100 000 mPas. Preferably it varies in the range of 1000 - 50 000 mPas, and more preferably in the range of 2000 – 15 000 mPas.

Another method according to the present invention comprises spinning or drawing the fibre from a spinning sol, wherein the viscosity of the silica sol is below 100 000 mPas, preferably in the range of 1000 – 50 000 mPas, and more preferably in the range of 2000 – 15 000 mPas.

The controllably biodegradable silica fibre of the present invention is spun from a silica sol, the biodegradation of the fibre being controlled by controlling the viscosity of the spinning sol or by controlling the starting point of the spinning process by the viscosity of the silica sol. Specifically, the fibres are spun from a silica sol having the viscosity of 1000 - 50 000 mPas, preferably 2000 – 15 000, the fibres having the solubility of 0.01 – 20 m-%/h , preferably 0.02 – 8.5 m-%/h in the simulated body fluid, respectively.

The silica sol can be prepared for example as described in WO 97/45367. For example, a silica sol can be prepared by allowing a silica-alkoxide, such as tetraethylorthosilicate (TEOS) or an organically modified silicate (ORMOSIL), to react with water and optionally an organic solvent, e.g. ethanol or polyethylene glycol, or a combination of solvents, at low temperature, such as -20 °C to 100 °C, preferably near room temperature, in the presence of an acidic or a basic catalyst by hydrolysis and subsequent condensation reactions. The condensation may also be partial. The sol can be incorporated with ions, such as Na, K, Ca, P, Mg, Al and B. The catalyst should be such that it would not harm the biologically active agent.

The methods that can be used for preparing the silica fibres according to the present invention are known to those skilled in the art. A suitable method is any method suitable for preparing fibres from silica sol, and the term spinning is used in this context to describe any such method. The spinning techniques include, e.g., dry spinning or a centrifugal method. In the dry spinning method, the silica sol is forced through a spinneret and the evaporation of the solvent promotes the gelation. For example, the spinning solution is kept in a closed container and an inert gas, preferably nitrogen gas, is led to the container to push the spinning solution to a gear pump, wherein the spinning solution is metered to the spinneret. Preferably, the container is temperature adjustable. There are also special methods that are based on dry spinning. These methods include, e.g., a method wherein the fibre is led to a

suitable aerosol which promotes the gelation of the fibre or a method wherein dry spinning and wet spinning are combined. In the centrifugal method, the spinning solution is in a rotating chamber which extrudes fibers through the holes in the chamber wall.

The controllably biodegradable fibres of the present invention can be used for delivery devices or pharmaceutical preparations that are, for example, implanted or injected into, or mucosally attached to a human or animal. Administration into any tissue, soft tissues or bone, is possible. This allows local application so that targeting of the biologically active agent release site is possible. Therefore, the maximum effect from the agent is received.

In this connection, a delivery device includes a silica fibre or a combination of silica fibres with a biologically active agent incorporated into the silica fibre structure. A pharmaceutical preparation, such as a granulate or capsule, in this context is a preparation that comprises the delivery device and possibly additional excipients useful in pharmaceutical preparations. A medical device of the invention is also useful for orthopedic and surgical purposes and need not contain a biologically active agent incorporated into its structure. A medical device may be, e.g., a woven or nonwoven mat made of silica fibres, a knitted fabric or a braired cord. The delivery devices and medical devices of the invention can be prepared by spinlaying.

The controllably biodegradable silica fibres of the invention may be either stable fibres or filaments. The silica fibres can be a part of a fibre blend or a part of some other material that is not in the fibre form.

Introduction of biologically active agents into the porous structure of the fibre provides alternatives for the design of biomedical applications. Biodegradable and non-toxic materials that are able to work directly and locally in the human or animal are beneficial, for example as implants used as drug delivery device or temporary implants in bone repairs. The sol-gel derived silica fibres according to the invention fulfill these requirements. The biologically active agents incorporated into the fibre structure are released controllably and they can be used for delivery devices or pharmaceutical preparations that are, for example, implanted or injected into, or

mucosally attached to a human or animal. The biologically active agent can be any organic or inorganic agent that is biologically active. The biologically active agent can be, e.g., a medicine, a protein, a hormone, a living or dead cell, a bacteria, a virus or a part thereof. Biologically active agents include those especially useful for long-term therapy, such as hormonal treatment, e.g., contraception and hormone replacement therapy and for the treatment of osteoporosis, cancer, epilepsy, Parkinson's disease, pain, and cognitive dysfunction. The suitable biologically active agents may be, e.g., anti-inflammatory agents, anti-infectives (e.g., antibiotics and antiviral agents, such as glindamycin, miconazole), analgesics and analgesic combinations, antiasthmatic agents, anticonvulsants (e.g., oxycarbazepine), antidepressants, antidiabetic agents, antineoplastics, anticancer agents (e.g., toremifene, tamoxifene, taxol), antipsychotics, antispasmodics, anticholinergics, sympatomimetics, cardiovascular preparations, antiarrythmics, antihypertensives, diuretics, vasodilators, CNS (central nervous system) drugs such as antiparkinsonism dugs (e.g., selegiline), steroidal hormones (e.g., estradiol, progesterone, nestorone), sedatives (e.g., medetomidine, dexmedetomidine, levomedetomidine), tranquilizers, and cognitive dysfunction drugs (e.g., atipamezole). The medicine can be in the form of a salt, such as selegiline hydrochloride, (-)-4-(5-fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole hydrochloride, 4-(5-fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole hydrochloride, dexmedetomidine hydrochloride and toremifene citrate. The medicine can also be in the form of a free acid, such as ibuprofen; a free base, such as caffeine or miconatzole; or a neutral compound, such as Z-2-(4-(4-chloro-1,2-diphenyl-but-1-enyl)phenoxy) ethanol. A peptide can be e.g. levodopa, and a protein can be e.g., an enamel matrix derivative or a bone morphogenetic protein. An effective amount of a biologically active agent can be added to the reaction mixture at any stage of the process. For example, it can be mixed with the starting materials. It can also be added to the reaction mixture at the sol-stage before condensation reactions take place or during the condensation reactions, or even afterwards. The precise amount employed in a particular situation is dependent upon numerous factors, such as the method of administration, type of mammal, the

condition for which the biologically active agent is administered, the particular biologically active agent used, the desired duration of use, etc.

The following examples are merely intended to ilustrate the present invention and not in any way to limit its scope.

EXAMPLES

Example 1

Preparation of silica sols for spinning

The silica sols were prepared from TEOS (tetraethyl orthosilicate 98%, ALDRICH), deionised water (conductivity ~0.05 S), ethanol (Aa, 99.5%, ALKO) and HNO_3 (65%, Merck) or NH_3 (28%, Fluka) as catalysts using the sol-gel method. The molar ratios used are shown in Table 1.

Table 1. Sol compositions in molar ratios

	Molar ratio (r)			
Name	H_2O/ TEOS	EtOH/ TEOS	HNO/ TEOS	NH_3/ TEOS
FIB1 (A&B)	2	1	0.036	0
FIB2 (A&B)	2	1	0.1	0
FIB3	2	1	0.1	0.01

The spinning solution was prepared as follows. Ethanol was mixed with TEOS and nitric acid with water. The acid/water solution was added to the TEOS/ethanol solution under vigorous stirring and then the solution was poured in an evaporating dish. The lid of the dish is a special cooler which condenses the evaporating ethanol and leads it to a volumetric flask. The evaporating dish was placed into a water bath (40°C) and the solution was kept there until a desired amount of ethanol had evaporated (20-22 h). Evaporation of ethanol was used to reduce the overall process time after which all the sols were still spinnable. Table 2 shows theoretical silica concentrations of the spinning solutions assuming that the net reaction is $nSi(OR)_4 + 2nH_2O \rightarrow nSiO_2 + 4nROH$ and that the evaporating fraction

consists mostly of ethanol due to relatively low temperature and low water content (r=1) that is mostly consumed in the hydrolysis.

Table 2. Silica content of the spinning solution

Sample name	*$m(SiO_2)/[m(SiO_2)+ m(EtOH)]$ / wt-%*
FIB1_A	45.4
FIB1_B	45.4
FIB2_A	42.7
FIB2_B	42.7
FIB3	41.7

The sols were cooled to either 20°C or 0°C depending on the sample. When the spinning solution reached a certain level of viscosity the spinning was started. A rotational viscometer with a disc shaped spindle (Brookfield LVDV II+) was used to define the point where the spinning was started. Because of practical problems due to a great batch size of the spinning sols, the obtained viscosity values were not absolute, but they were comparable to each other. The initial viscosity was the same for all sample sols when the spinning process was started. However, each sol recipe was used to spin fibres in several stages. Air bubbles were removed from the spinning solution under partial vacuum. If this had not been done the sol-gel filaments would have broken due to a discontinuous flow of the spinning solution.

Dry spinning was used to prepare the sol-gel fibres. The spinning solution was kept in a container whose temperature is adjustable. Nitrogen gas was led into the closed container to push the spinning solution to a gear pump. Nitrogen is a good choice for this purpose because then the spinning solution is prevented to contact the humid air. The gear pump (Zenith 958736) with a capacity of 0.6 ml/revolution metered the spinning solution to the spinning head. The spinneret is made of a gold/platinum mixture. The diameter of the holes was 0.065 mm and the length/diameter (l/d) ratio was 1. The number of the holes was 6. The distance between the spinneret and the wind-up roll was adjusted to meet the demands of each

fibre.

Example 2

Characterisation of the fibre structures

A thermogravimetric analysis (TGA) was performed on the green state fibres to measure weight changes with a Netzsch TG-209 equipment (NETZSCH GmbH, Selb, Bavaria, Germany) with nitrogen as the protective gas and air as the purge gas. The sample holder was a ceramic alumina crucible and the background measurement was done with an empty crucible before the measurements. The mass loss during the heat-treatment of the fibres was measured with a temperature program including several steps, both isothermal and dynamic: isothermal for 15 min at 21°C, dynamic 21-150°C with 2°C / min, isothermal for 60 min at 150°C, dynamic 150-700°C with 5°C / min and isothermal at 700°C for 30 min. TGA was performed for the fibres aged in a desiccator at room temperature for 3 months. The analysis was done up to 700°C because higher temperatures are practically useless concerning biodegradable applications of silica. The results of the samples are shown in Figure 1, and the derivative of the spectra is shown in Figure 2.

The physical appearance of the fibres and the quality of the fibre filament in the spinning process, shown in Table 2, seem to have a connection with the TGA measurements. The mass losses of the fibres were quite considerable (15-25%), which stresses that a careful control of the heat treatment is required in order to avoid cracking problems. The mass losses of the fibres spun in the early stage of spinnability was not as great as those spun in the later stage of spinnability. The greatest difference started at about 300°C, where the organic matter usually starts to evaporate. Because the recipes were exactly the same for FIB1_A and FIB1_B, as well as for FIB2_A and FIB2_B, respectively, it is likely that some organic matter was captured in the fibre structure in the fibres spun in the early stage. Also the shift observed in the derivatives of the fibres spun in the later stage of spinnability (FIB1_B, FIB2_B and FIB3) indicates some differences in the evaporation of the organic matter and in the fibre structure. The physical appearance of the fibres contributes suggestions. The black colour of the fibres spun in the early stage of

spinnability indicate that they contain carbon residuals. FIB3, where both HNO_3 and NH_3 were used as catalysts, had intermediate properties, both in the TG analysis and physical appearance. The mass loss is greater than in FIB1_A and FIB2_A, but smaller than in FIB1_B and FIB2_B. Also the colour of the FIB3 fibre was something between white and black, i.e., brown, and the filament quality in the spinning process had analogous properties. The best and continuous fibres were easiest achieved with FIB1_B and FIB2_B. Thre were some difficulties with FIB3, FIB1_A and FIB2_A (processed at 0°C to achieve high enough viscosity in spinning). The filament broke easily and continuous fibre processing was more difficult.

The infrared absorption spectra were recorded between 400 and 4000 cm^{-1} using Bruker IFS 66 FTIR spectrometry. The measurements were carried out with the Diffuse Reflectance Infrared Fourier Transformation (DRIFT) system. Potassium bromide was used as a background material. The resolution of the FTIR equipment was 4 cm^{-1}. The FT-IR measurements made for the fibres heat-treated in the thermogravimetric analysis are shown in Figure 3. The measurements gave information of the typical OH groups on the silica surface, but also two unusual peaks were detected in the fibres spun in the early stage of spinnability (FIB1_A and FIB2_A). The broad peak at 3400-3770 cm^{-1} includes peaks related to isolated single SiOH groups, isolated geminal groups, H-bonded hydroxyls and physically adsorbed water which additionally has a peak approximately at 1630 cm^{-1} (broad). Additionally, the shift in the peaks indicated by a line drawn in the graph suggested that some organic residuals were also detected here. The shift was analogous with the extra peaks observed for FIB1_A and FIB2_A and the slight shift for FIB3 contributed the intermediate physical appearance. Peaks related to Si-O-Si vibrations were observed at 1200-1100 (broad) and 800 cm^{-1}. The peaks at 1870 and 2000 cm^{-1} were the Si-O-Si overtone bands of silica. The peak at 1300-1400 cm^{-1} was not typical for silica, but NO_3^- stretching vibration was typically located there. The catalyst used in the sol preparation process was HNO_3, which may have residuals left in the structure. The fibre structure was commonly condensed and the temperature increased from 450 to 700°C quite fast and was kept there only for 30 min. This means that the

decomposition of nitrate was not very effective. The two interesting peaks at 2330 and 3050 cm^{-1} were clearly seen only for FIB1_A and FIB2_A, but they could not be directly related to any component present in the system. The only possibility was that the fibres contained carbon residuals which formed double bonds with hydrogen (3050 cm^{-1}) and oxygen (2330 cm^{-1}) observed at these points.

A scanning-transmission electron microscopy (JEOL, JEM 1200 EX) was used to illustrate the bulk structure of the green state fibres. The fibres were embedded in an epoxy resin (EPON 812). Propylene oxide was used as a solvent and epoxy embedding media DMP-30 and DDSA or MNA as an accelerator and hardeners (FLUKA), respectively. The hardened samples were cut with an ultramicrotome to a thickness of 60-70 nm and the cross sections of the fibres were analysed.
A transmission electron micrograph of the cross section of FIB2_B is shown in Figure 4. The image was chosen as an example to show the inner structure of the sol-gel derived silica fibres. The images of all five samples reminded each other. FIB2_B was suggested to be a representative example of the fibres because the filament quality was good and the fibres were easy to prepare. The white bar at the bottom of the image corresponds 20 nm. The structure was typical for the sol-gel derived materials. The structure was not completely condensed, but it contains a lot of small pores of about 2-5 nm in diameter, which indicates that structure is formed from smaller silica units.

Example 3

Biodegradation of Fibres

The spinning viscosity as a function of the starting point of the spinning process is presented in Figure 5. The graph decribes schematically the viscosity levels of the spinning sols and ageing times for the fibres FIB1, FIB2 and FIB3 before the biodegradation test in the simulated body fluid. The spinning viscosities are roughly divided into three levels (η (1) =2000-3500 mPas, η (2) =3500 - 7500 mPas, and η (3) >7500 mPas.

The biodegradation of the samples was studied *in vitro* using a simulated body fluid (SBF). The simulated body fluid was prepared by dissolving the reagent chemicals of NaCl, $NaHCO_3$, KCl, $K_2HPO_4 \cdot 3H_2O$, $MgCl_2 \cdot 6H_2O$, $CaCl_2 \cdot 2H_2O$ and Na_2SO_4 into deionised water. The fluid was buffered at a physiological pH 7.40 at

37°C with tris(hydroxymethyl)aminomethane and hydrochloric acid (Ohtsuki, C, et al., *J. Non-Cryst. Sol.*, 143 (1992) 84-92).

Three pieces of each specimen were used to study the reactions of the sol-gel derived silica fibres in SBF. Each sample (10 mg) was immersed in 50 ml of SBF contained in a polyethylene bottle covered with a tight lid. Three samples of SBF enclosed in bottles without a specimen were used as controls to examine the solution stability. The samples were immersed in the SBF fluid for 2 weeks, the bottles being placed in a shaking water bath (SBD 50 (stroke 36 mm, speed = 160strokes/minute)) having a constant temperature at 37°C. Sample solutions were monitored for silicon and calcium concentrations as a function of immersion time. The calcium concentrations were determined with atomic absorption spectrophotometer (AAS, Perkin-Elmer 460). The silicon concentrations were analysed by a molybdenum blue-method (Koch, O.G. & Koch-Dedic, G.A., Siliconmolybdänblau-Verfahren. In *Handbuch der Spurenanalyse.* Springer-Verlag (1974), p. 1105) based on reduction with 1-amino-2-naphtol-4-sulfonic acid using a UV-Vis spectrophotometer (Hitachi Model 100-60). All samples were tested three times each in order to avoid inaccuracy problems and possible degradation differences depending on the distribution in the cross-sectional diameter of the fibres (30-80 m, medium value 50 m). The biodegradation (in vitro in the simulated body fluid) of the green state fibres FIB1_A, FIB1_B, FIB2_A, FIB2_B, and FIB3 aged for about one and three months is summarised in Table 3.

Table 3.

Silica solubility of the fibers soaked in the SBF

Fiber Name	*Aging time / Months*	*Silica solubility in SBF / wt% / h**
FIB1_A	1	0.02
FIB2_A	1	0.03
FIB1_B	1	(0.8)**
FIB2_B	1	(0.9)**
FIB3	1	1.7
FIB1_A	3	0.03
FIB2_A	3	0.2
FIB1_B	3	0.7
FIB2_B	3	0.8
FIB3	3	1.4

* Calculated from the linear portion of the curves before the saturation level between 5 to 53 h of immersion.

**Estimation, the point at ~50 h is missing due to technical problems.

The same kind of analogy observed in the TG analysis and FT-IR measurements was also observed here. The fibres spun in the early stage of spinnability (FIB1_A and FIB2_A) degraded very slowly when compared to fibres spun in the later stage (FIB1_B, FIB2_B). FIB3 again had some kind of intermediate properties. According to the obtained results, some kind of plateau value or a saturation level was achieved after few days of immersion in theSBF. The solubility rates (before the plateau level) of FIB1_B, FIB2_B and FIB3 were clearly faster than for FIB1_A and FIB2_A. This indicates that the area of silica available for the degradation is greater in the structure of the fibres spun in the later stage of spinnability. As observed in Table 3, there were some differences in the degradation if the samples aged for 1 or 3 months were compared to each other. A clear difference was observed in FIB2_A. The rate of solubility was greater for the sample aged for 3 months, as was the silica saturation level (~2 % for the sample aged for 1 month and ~5% for the sample aged for 3 months). For the fibres spun in the later stage (FIB1_B, FIB2_B and FIB3) there were no significant differences after 1 or 3 months of aging. The values were practically the same indicating that the structures were quite stable.

However, they all were clearly more soluble in the SBF than the fibres spun in the early stage of spinnability.

In Figure 6, the biodegradation of the green state fibres FIB1_A, FIB1_B, FIB2_A, FIB2_B, and FIB3 aged for about three months is presented.

Further, the biodegradation of fibres FIB1, FIB2 and FIB3 *in vitro* in the SBF is presented in Figures 7 to 12. In figures 7 and 8, the biodegradation of the fibre FIB1 aged for about two weeks, and three, five and 6.5 months is presented. The biodegradation of the fibre FIB2 aged for about two weeks, and two, three, and five months is presented in Figures 9 and 10. Further, the biodegradation of the fibre FIB3 aged for about two weeks, three, four and five months is presented in Figures 11 and 12.

The influence of the starting point of the spinning process to the biodegradation of the fibres is clear. The main parameters, which affect the viscosity, are the concentration, lenght and degree of branching of silica polymers. In turn, these factors affect the formation of fibre structure, e.g., packing and orientation of silica polymers, and result in different biodegradation.

The fibres derived from the sols which have low viscosity during the the spinning process degrade slower than fibres derived from sols prepared at higher spinning viscosity. Accordingly, the starting point of the spinning process is important regarding the biodegradation. The fibres spun from in the early stage of spinnability degraded very slowly as compared to fibres spun in the later stage.

It was observed that the solubility rate of FIB1 (determined from the linear portion of the corresponding solubility curves) was lower at very high spinning viscositsies, although the saturation levels did not change significantly. This is assumed to occur because the slightly thinner fibres with smoother surfaces which are produced at very high spinning viscosities.

In Figure 13 the changes of SiO_2-concentration (wt-%) as a function of immersion time in the simulated body fluid for different fibres are presented. These results show that a wide range of different solubilities is covered by adjusting the propertities of the silica sol.

Example 4

Preparation of silica fibres containing dexmedetomidine hydrochloride

A sol for the fiber spinning was prepared from TEOS, deionized water, ethanol and HNO_3 as a catalyst in 1/2.35/1/0.000322 ratio using the sol gel method. Ethanol was mixed with TEOS and nitric acid with water. The acid/water solution was added to the TEOS/ethanol solution under vigorous stirring and then the solution was poured in an evaporating dish. The evaporation process was performed as described in Example 1. Dexmedetomidine hydrochloride (HCl) was added after the ethanol evaporation (corresponding to 1 wt-% in dried fibre). Viscosity was 5600 mPas when the spinning process was started. The fibres were spun at four different stages of spinnability at 20°C. The fibres were packed and stored air tightly in aluminium folio bags at room temperature until the dissolution tests were carried out.

***In vitro* dissolution test**

The dissolution profiles of dexmedetomidine HCl from the silica fibres were studied using dissolution apparatus II (paddle method, Sotax AT6, Basel, Switzerland). Each sample (50 mg) was immersed in 250 ml of 0.9 wt-% NaCl solution. The rotation speed was 50 rpm and the temperature 37°C. Dissolved dexmedetomidine HCl in the dissolution samples was measured on an UV-visible spectrophotometer (Hewlett Packard 845/A, USA) at the maximum absorbance of dexmedetomidine HCl, 220 nm.

Results

The release of dexmedetomidine HCl showed a burst (33%) at the spinning viscosity lower than 10 000 mPas (Figure 14).When the spinning viscosity was increased to more than 11500 mPas, the burst effect was decreased to 3- 10 %. At spinning viscosity above 11500 mPas the release rate of dexmedtomidine HCl was decreased compared to fibres spun lower than 11500 mPas.

Those skilled in the art will recognize that while specific embodiments have been illustrated and described, various modifications and changes may be made without departing from the spirit and scope of the invention.

The references discussed herein are specifically incorporated by reference in their entity.

Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention discolsed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

CLAIMS

1. A method for preparing a controllably biodegradable silica fibre, comprising spinning the fibre from a silica sol, wherein the starting point of the spinning process is controlled by the viscosity of the silica sol.

2. The method according to claim 1 wherein the viscosity of the silica sol at the starting point of the spinning process is below 100 000 Pas.

3. The method according to claim 2 wherein the viscosity of the silica sol at the starting point of the spinning process is from about 1000 to about 50 000 mPas.

4. The method according to claim 3 wherein the viscosity of the silica sol at the starting point of the spinning process is from about 2000 to about 15 000 mPas.

5. A method for preparing a controllably biodegradable fibre, comprising spinning the fibre from a spinning sol having a viscosity below 100 000 mPas.

6. The method according to claim 5 wherein the viscosity of the spinning sol is from about 1000 to about 50 000 mPas

7. The method according to claim 6 wherein the viscosity of the spinning sol is from about 2000 to about 15 000 mPas.

8. A controllably biodegradable silica fibre spun from silica sol, the biodegradation of said fibre being controlled by controlling the starting point of the spinning process by the viscosity of the silica sol.

9. The controllably biodegradable fibre according to claim 8, wherein the viscosity of the silica sol at the starting point of the spinning process is below 100 000 mPas.

10. The controllably biodegradable fibre according to claim 9, wherein the viscosity of the silica sol at the starting point of the spinning process is from about 1000 to about 50 000 mPas.

11. The controllably biodegradable fibre according to claim 10, wherein the viscosity of the silica sol at the starting point of the spinning process is from about 2000 to about 15 000 mPas.

12. A controllably biodegradable silica fibre spun from a silica sol, the biodegradation of the fibre being controlled by controlling the viscosity of the spinning sol.

13. The controllably biodegradable fibre according to claim 12, wherein the viscosity of the spinning sol is below 100 000 mPas.

14. The controllably biodegradable fibre according to claim 13, wherein the viscosity of the spinning sol is from about 1000 to about 50 000 mPas.

15. The controllably biodegradable fibre according to claim 14, wherein the viscosity of the spinning sol is from about 2000 to about 15 000 mPas.

16. A method for controlling the biodegradation of a silica fibre spun from a silica sol, wherein by the method comprises controlling the viscosity of the spinning sol.

17. The method according to claim 16 wherein the viscosity of spinning sol is below 100 000 mPas.

18. The method according to claim 17 wherein the viscosity of spinning sol is from about 1000 to about 50 000 mPas.

19. The method according to claim 18 wherein the viscosity of spinning sol is from about 2000 to about 15 000 mPas.

20. A method for controlling the biodegradation of a silica fibre spun from a silica sol, wherein the method comprises controlling the viscosity of the silica sol at starting point of the spinning process.

21. The method according to claim 20 wherein the viscosity of the silica sol at the starting point of the spinning process is below 100 000 mPas.

22. The method according to claim 21 wherein the viscosity of the silica sol at the starting point of the spinning process is from about 1000 to about 50 000 mPas.

23. The method according to claim 22 wherein the viscosity of the silica sol at the starting point of the spinning process is from about 2000 to about 15 000 mPas.

24. A delivery device comprising the controllably biodegradable fibre according to any one of claims 8 – 15, wherein the fibre contains a biologically active agent.

25. The delivery device according to claim 24, wherein said biologically active agent is a medicine, a protein, a hormone, a living or dead cell, a bacteria, a virus or a part thereof.

26. The delivery device according to claim 25, wherein said biologically active agent is a medicine.

27. A pharmaceutical preparation comprising a delivery device according to any one of claim 24-26 .

28. A method for administering a biologically active agent into a human or animal, wherein said method comprises implanting, injecting , or mucosally attaching a delivery device, wherein said delivery device comprises a controllably biodegradable fibre and wherein the fibre comprises a biologically active agent.

29. The method according to claim 28, wherein the biologically active agent is administred into a mammal.

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(71) Applicants and
(72) Inventors: **JOKINEN, Mika** [FI/FI]; Mielikinkatu 5, FIN-20540 Turku (FI). **PELTOLA, Timo** [FI/FI]; Jaakkimankatu 5 D 33, FIN-20740 Turku (FI). **VEITTOLA, Sinikka** [FI/FI]; Elementinpolku 17 B 24, FIN-33720 Tampere (FI). **AHOLA, Manja** [FI/FI]; Iltatähdentie 4 as 91, FIN-20200 Turku (FI). **KORTESUO, Pirjo** [FI/FI]; Pohjantähdentie 4 B 38, FIN-20200 Turku (FI).

(74) Agent: **TURUN PATENTTITOIMISTO OY**; P.O. Box 99, FIN-20521 Turku (FI).

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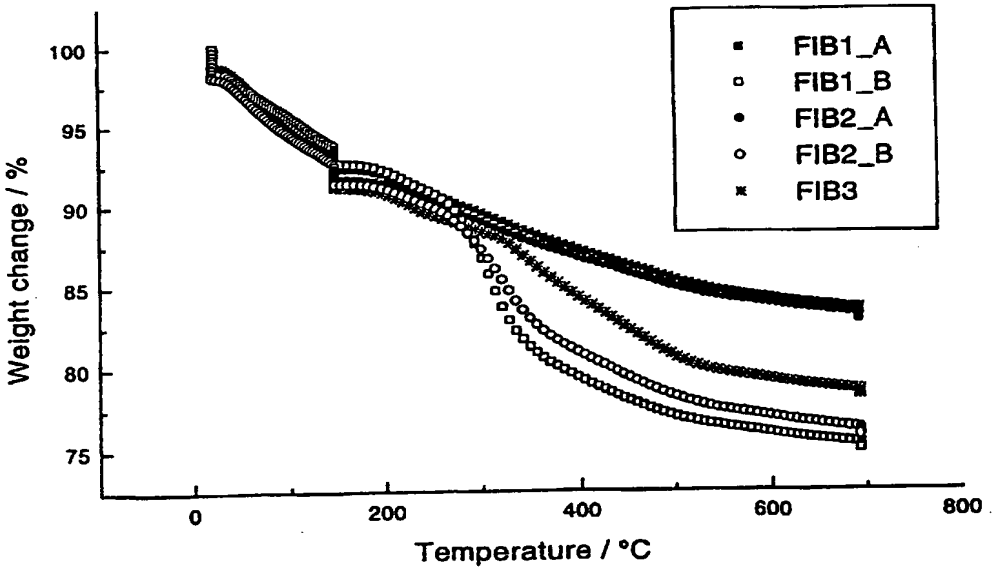

(57) Abstract: The present invention relates to a method for preparing controllably biodegradable silica fibres. The method comprises spinning the fibres from a silica sol, the viscosity of the sol being controlled. Further, the present invention relates to controllably biodegradable silica fibres prepared according to the invention and methods for controlling the biodegradability of the fibres. The invention also relates to controllably biodegradable fibres as sustained and/or controlled release delivery devices for biologically active agents, and to pharmaceutical preparations comprising such devices.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

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EPO-Internal, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 196 09 551 C (FRAUNHOFER GES FORSCHUNG) 17 July 1997 (1997-07-17) column 2, line 61 -column 3, line 15; claims 1-3 abstract	1-23
Y		24-27

X	US 4 965 128 A (GREIDANUS PIETER J ET AL) 23 October 1990 (1990-10-23) column 1, line 8 - line 20; claim 1 abstract	28,29
Y		24-27

X	EP 0 253 554 A (PFIZER) 20 January 1988 (1988-01-20) abstract; claims 1-4	28,29
A		24-27

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[X] Further documents are listed in the continuation of box C.

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Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	M. Arvidsson

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 342 595 A (DAVIDOVITS JOSEPH ET AL) 30 August 1994 (1994-08-30) claims 1-20 abstract	1-23
A	US 4 895 709 A (LAINE RICHARD M) 23 January 1990 (1990-01-23) column 2, line 35 -column 2, line 60 abstract	1-23
A	WO 96 14274 A (JENSEN SOREN LUND) 17 May 1996 (1996-05-17) claims 1-3,5,12 abstract	1-23
A	WO 97 45367 A (ORION-YHTYMÄ OY ET L) 4 December 1997 (1997-12-04) claims 1-6 abstract	1-29
A	EP 0 336 014 A (VECTORPHARMA INT) 11 October 1989 (1989-10-11) column 5, line 1 -column 6, line 36 abstract	1-29
A	WO 95 28124 A (ATRIX LAB INC) 26 October 1995 (1995-10-26) abstract; claims 30-32	24-29

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 00/00131

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/FI 00/00131

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-23

   The invention according to claims 1-23 relates to method for producing a biodegradable fibre from a silica sol, comprising that the viscosity of the silica sol is controlled at the starting point of the spinning process.

2. Claims: 24-29

   The invention according to claims 24-29 relates to a biodegradable fibre, wherein the fibre contains a biologically active agent.

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No
PCT/FI 00/00131

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/FI 00/00131

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		US 5707647 A	13-01-1998
		US 5717030 A	10-02-1998

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
FIBRE		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/FI 00/00131	21/02/2000	22/02/1999
Applicant		
JOKINEN, Mika		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [X] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 1

   [ ] as suggested by the applicant.

   [X] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 00/00131

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [X] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

[X] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-23

   The invention according to claims 1-23 relates to method for producing a biodegradable fibre from a silica sol, comprising that the viscosity of the silica sol is controlled at the starting point of the spinning process.

2. Claims: 24-29

   The invention according to claims 24-29 relates to a biodegradable fibre, wherein the fibre contains a biologically active agent.

INTERNATIONAL SEARCH REPORT

[redacted]ational Application No
[redacted]T/FI 00/00131

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C03C13/06 C03B37/04 A61K47/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C03C C03B A61F A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 196 09 551 C (FRAUNHOFER GES FORSCHUNG) 17 July 1997 (1997-07-17) column 2, line 61 -column 3, line 15; claims 1-3 abstract	1-23
Y	---	24-27
X	US 4 965 128 A (GREIDANUS PIETER J ET AL) 23 October 1990 (1990-10-23) column 1, line 8 - line 20; claim 1 abstract	28,29
Y	---	24-27
X	EP 0 253 554 A (PFIZER) 20 January 1988 (1988-01-20) abstract; claims 1-4	28,29
A	---	24-27
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 November 2000	06. 02. 01

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	M. Arvidsson

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 342 595 A (DAVIDOVITS JOSEPH ET AL) 30 August 1994 (1994-08-30) claims 1-20 abstract	1-23
A	US 4 895 709 A (LAINE RICHARD M) 23 January 1990 (1990-01-23) column 2, line 35 -column 2, line 60 abstract	1-23
A	WO 96 14274 A (JENSEN SOREN LUND) 17 May 1996 (1996-05-17) claims 1-3,5,12 abstract	1-23
A	WO 97 45367 A (ORION-YHTYMÄ OY ET L) 4 December 1997 (1997-12-04) claims 1-6 abstract	1-29
A	EP 0 336 014 A (VECTORPHARMA INT) 11 October 1989 (1989-10-11) column 5, line 1 -column 6, line 36 abstract	1-29
A	WO 95 28124 A (ATRIX LAB INC) 26 October 1995 (1995-10-26) abstract; claims 30-32	24-29

INTERNATIONAL SEARCH REPORT

[redacted]tion on patent family members

[redacted]national Application No
[redacted]CT/FI 00/00131

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 19609551 C	17-07-1997	NONE	
US 4965128 A	23-10-1990	NL 8401912 A	02-01-1986
		AT 73649 T	15-04-1992
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EP 0253554 A	20-01-1988	AU 574955 B	14-07-1988
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		JP 63023815 A	01-02-1988
		KR 9000512 B	31-01-1990
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INTERNATIONAL SEARCH REPORT

[redacted]ation on patent family members

[redacted]national Application No
[redacted]CT/FI 00/00131

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